AD_____

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TITLE: Prehospital Use of Plasma for Traumatic Hemorrhage

PRINCIPAL INVESTIGATOR: Bruce D.Spiess

CONTRACTING ORGANIZATION: Virginia Commonwealth University
Richmond, VA 23298

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14. ABSTRACT

There are no significant research findings to report during this period. The university's Institutional Review Board (IRB) has recently granted approval to begin community consultation activities. Work is ongoing to secure FDA approval for an investigational New Drug (IND) application. Work toward developing standards of operation for the Virginia Commonwealth University Health Systems Bold Bank and the Richmond Ambulance Authority and the County of Henrico Emergency Services is continuing.

15. SUBJECT TERMS- none provided

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Table of Contents

Introduction

The contract for our project entitled Prehospital Use of Plasma for Traumatic Hemorrhage was awarded June 1, 2012. The period from June 1, 2012 to May 31, 2013 has largely involved dealing with regulatory approvals that are required prior to enrolling patients. These have included multiple submissions, queries, responses and in-person question and answer sessions with the VCU-Institutional Review Board (IRB). Copies of the initial submission and re-submission were sent to the Program Manager as requested. There has been written and telephone discussions with the United States Food and Drug Administration (US-FDA) regarding the Investigational New Drug application (IND). A budget revision was submitted and approved to provide sub-awards to the County of Henrico and The Richmond Ambulance Authority. There have been numerous communications and meetings with both entities over the period.

Body

IRB approval: July and August 2012 were spent writing the VCU IRB forms. These were requested in 25 hard copies which were submitted on September 12, 2012. The IRB had extensive and fundamental changes requested. After in-person meetings in November the requested changes were submitted on December 3, 2012. That was followed by in-person appearance of the PI to the IRB on January 24, 2013, again with requested multiple changes. In all the PI and or other investigators, lead nurse researcher and team members have met in person with the IRB 4 times in year 1. The VCU IRB approved community consultation activities on April 11, 2013 (Appendix 1). Additional IRB community consultation activities changes were approved by the VCU IRB on May 23, 2013 (Appendix 2).

FDA-IND: Telephone discussions with the FDA were held prior to our submission of the grant proposal. Further in-depth written correspondence was carried out between our blood bank and the US FDA in September 2012 which triggered an internal FDA meeting. Correspondence from the FDA was received October 5, 2012 (Appendix 3) in which they answered a number of our questions regarding how we should/could position an IND application. Of note there has been confusion regarding whether we could proceed with both regulatory agencies (IRB and US FDA) in parallel or in sequence. It has been our understanding that we were to proceed with our IRB and only after receiving initial approval from them could we then approach the FDA.

Staff of VCU Health System's blood bank have been working with the PI in answering/addressing the FDA IND questions and responses. We are working on the logistics for how we will move thawed plasma through our medical system, how it will be monitored and how it will be returned into the general use pool if not utilized during its 24 hours on the supervisor's vehicle. The blood bank is working on SOP's and teaching our personnel to work with the EMT's who will be directing the use of plasma. The blood bank expressed concern about the logistics of placing thawed plasma in all 6 supervisor's cars at once meaning that 12 units of plasma will be out in the field at any one time. We decided to start with one supervisor's car per shift carrying the thawed plasma and see that our logistics are working before we build up to the potential of every 24 hours having to change out 12 units of plasma and feed them back into the hospital system if not utilized. We understand that by starting small (one car per region) we may initially miss potential patients but we wish not to waste products and not to tax the system until we see that we have a working process.

Henrico County and Richmond Ambulance Authority:

The medical director of the EMS system for Henrico County has been working within the county government organization to create consistency between the protocols as originated, revised and finalized and what the EMS

supervisors understand. Multiple face to face meetings have occurred some with the PI in attendance and others with the medical director. Sub-contracts have been negotiated and vetted through county legal oversight and are now in place awaiting further work once the IND and IRB processes are completed. The next steps with the two EMS systems are to purchase and mount refrigeration units the supervisor's vehicles and begin training of the front end providers on handling thawed plasma as well as regulatory documentation. We are working with the VCU Blood Bank regarding the development of standard operating procedures (SOP).

Key Research Accomplishments

There are no key research accomplishments to report at this time. We will begin community consultation activities in quarter 1 and continue those activities into quarter 2 of year 2. We will also continue to work with the VCU IRB and the FDA for regulatory approvals to continue the study and anticipate that enrollment of patients will begin in early 2014 (quarter 3).

Reportable Outcomes

There are no reportable outcomes at this time. We anticipate having data from community consultation activities to report in quarter 2 of year 2.

Conclusion

A great number of hours have been spent in IRB interactions and meetings. We are still engaged in the IRB and FDA IND process. We anticipate that the regulatory processes will be completed within the next several months and we will be able to train the EMT supervisors and begin enrollment of patients by early 2014.

References

No references at this time.

Appendices

See next page

APPENDIX 1

VIRGINIA COMMONWEALTH UNIVERSITY

Make it real.

VCU

Office of Research Subjects Protection
Bio-Tech Research Park, Building 1
800 E. Leigh St., Ste.#3000
P.O. Box 980568
Richmond, Virginia 23298-0568

DATE: April 11, 2013

TO: Bruce Spiess, MD
Anesthesiology

FROM: Andrea Hastillo, MD Andrea Hastillo MD
Chairperson, VCU IRB Panel C
Box 980568
April 11, 2013

RE: **VCU IRB #: HM14813**
Title: Pre-Hospital Use of Plasma for Traumatic Hemorrhage (PHUPTH)

The following study involving the research use of human subjects was ***approved for community consultation*** by the VCU IRB on April 11, 2013 according to 21 CFR 50.24. The approval is for community consultation activities only. The changes requested by the Panel received in the Office of Research Subjects Protection on April 5, 2013 satisfactorily meet the stipulations set forth in the March 28, 2013 IRB Panel meeting.

This approval includes the following items reviewed by this Panel:

PROTOCOL: Pre-Hospital Use of Plasma for Traumatic Hemorrhage (PHUPTH) – Research Plan Template, Version Date 4-5-13-stamped received 4/5/13 *(provisionally approved pending outcome of community consultation)*

- Exception from Informed Consent Proposal: Community Consultation Plan; Version 2 dated 3/14/2013-stamped received 3/19/13
- Prehospital Use of Plasma for Traumatic Hemorrhage (PHUPTH Study) Community Consultation PowerPoint Presentation-stamped received 3/19/13
- Appendix 1: Print ad – Community Consultation, Version Date 8.3.2012-stamped received 3/19/13
- Appendix 2: Radio ad/psa 30-second – Community Consultation, Version Date 3.13.2013-stamped received 3/19/13
- Appendix 3: Opt-out bracelet wording, Version Date 8.3.2012-stamped received 3/19/13
- Appendix 4: Plasma Study Website text: Go.vcu.edu/Plasma, Version Date 3/15/13-stamped received 3/19/13
- Appendix 5: VCU Digital Signs, Version Date 8.3.2012-stamped received 3/19/13
- Appendix 7: TelegRam and VCUHS mass mail posting, Version Date 3.13.2013-stamped received 3/19/13
- Appendix 8: GRTC Bus Signs for rear of bus, Version Date 8.3.2012-stamped received 3/19/13
- Appendix 9: Broadcast Email, Version Date 3.13.2013-stamped received 3/19/13
- Appendix 10: Meeting announcement Email, Version Date 3.13.2013-stamped received 3/19/13
- Appendix 11: Meeting announcement flier, Version Date 3.13.2013-stamped received 3/19/13
- Appendix 12: General information flyer – Community Consultation, Version Date 3.13.2013-stamped received 3/19/13
- Appendix 13: Group Evaluation Survey, Version 2 dated 4/5/13-stamped received 4/5/13
- Appendix 14: Self-Administered Survey, Version 2 dated 4/5/13-stamped received 4/5/13

- Appendix 15: Social Media, Version Date 8.3.2012-stamped received 3/19/13
- Appendix 17: Opt-out wrist band response letter, Version Date 3.13.2013-stamped received 3/19/13
- Appendix 18: PHUPTH Grant PAID Marketing Plan: Community Consultation Phase, Version Date 8/29/2012-stamped received 3/19/13
- Appendix 20: Attempts to contact subject/LAR/family log, Version Date 12.5.2012-stamped received 3/19/13
- Appendix 23: Eliciting Refusal Script, Version 1 dated 3.7.13-stamped received 3/19/13

In addition, the IRB has ***acknowledged*** the following document:

- Appendix 6: Press Release, Version Date 03.13.2013-stamped received 3/19/13

IMPORTANT NOTES:

- The IRB must be notified of the date and time established for community consultation meetings. Transcriptions/minutes must be made of all the community consultation meetings and submitted to the panel for review.
- Please replace the phone numbers indicated with "xxx-xxxx" with the correct phone numbers in all applicable documents, and notify the panel of these numbers prior to printing.

If you have any questions, please contact Dr. Andrea Hastillo, Chairperson, VCU IRB Panel C, at ahastillo@mcvh-vcu.edu or 301-7698; or you may contact Ingrid Rosiuta, IRB Coordinator, VCU Office of Research Subjects Protection, at IRBPanelC@vcu.edu or 827-1446.

Exception from Informed Consent Proposal

Prehospital Use of Plasma for Traumatic Hemorrhage (PUPTH)
Principal Investigator: Bruce Spiess, M.D.

I. Introduction

Trauma is the leading cause of mortality for individuals under age 45 in the civilian population and uncontrolled hemorrhage (massive loss of blood) is a leading cause of death from trauma. When compared to cancer, heart disease and stroke, trauma results in significantly greater loss of productive years of life. For many reasons this study is of military importance as much as of great relevance to civilian trauma care.

Polytrauma (PTr) can result in severe hemorrhage and tissue hypoperfusion (tissues don't get enough oxygen) and may lead to a complex coagulopathy (blood clotting disorders). In addition the blood can become more acid-like (acidosis), and body temperature can become dangerously low (hypothermia). This coagulopathic state has been termed the Acute Coagulopathy of Trauma (ACoTS) or trauma induced coagulopathy (TIC).[3, 4, 5, 7, 8] Giving (transfusing) blood itself, although lifesaving, is not without risk. Overuse of transfusion may worsen outcomes and transfusion can lead to inflammation causing further problems to the PTr patients' picture. [9-32]

Coagulation: In the body, the balance between bleeding and thrombosis (clotting) is called homeostasis. Cellular proteins attach to platelets which then work together with certain other normal cells.[37-43] However, if the processes are not balanced and cause homeostasis to be too abnormal, then coagulation problems such as TIC can occur.[37,41]

Resuscitation Fluids: While control of hemorrhage (excessive bleeding) is vitally important in the treatment of the PTr victim, doing so in the prehospital combat or civilian environment when there is uncontrolled hemorrhage represents perhaps the most significant challenge to prehospital trauma care. Early restoration of a minimum level of tissue perfusion (oxygenation) is vital to survival in PTr without causing additional hemorrhage.[1, 2, 6, 33, 35] The amount of circulating blood, oxygen delivery, numbers of red cells (oxygen-carrying blood cells), and coagulation factor restoration are all important parts of the resuscitation of the victim of PTr. Fresh whole blood can be considered as the "gold standard" by which all other resuscitation fluids should be measured but of course as indicated above is not practical. [34]

What is becoming clear is that use of traditional massive crystalloid (e.g. normal saline [NS]) resuscitation can cause bleeding and/or complications that increase morbidity (negative effects on the body) and mortality. Attempts to correct these issues with other types of nonblood fluids have been repeatedly made.[44-56] While there is general agreement that civilian prehospital use of traditional crystalloids such as NS are not the best, they continue to be the standard of care.

Early replacement of lost plasma proteins is likely to be key for prevention of TIC in PTr and in maintaining tissue perfusion. In recent swine (pig) models of PTr, plasma has been demonstrated to more effective than crystalloids or other solutions that help increase volume of plasma in preserving tissue perfusion and nearly equal to fresh whole blood in preventing TIC and improving survival.[57]

Bridging the Gap: Given the benefits being demonstrated in use of plasma in PTr preclinical models coupled with the improvements in outcomes using massive transfusion protocols (MTPs; parts of blood – red blood cells, plasma, and platelets – are given in specific ratios) in clinical civilian and

combat trauma care, it is thus attractive to pose the far forward use of thawed human plasma (TP) for both combat casualty and civilian trauma care to optimize patients prior to definitive surgical intervention and to prevent such catastrophic complications such as TIC. The far forward trialing of TP in the civilian prehospital trauma setting lacks problems (regulatory and research) that currently cannot be overcome in the combat setting and has the potential for direct benefit to significantly enhance civilian prehospital trauma care. This can be viewed as a critical and vital bridging step, creating much needed new knowledge in the early treatment of the victim of PTr and in the development of new products and approaches to treatment.

To date, there has been no large scale human testing of TP vs. NS. Historical reports of good outcomes using plasma in WWII[56], not-withstanding, this proposal therefore stands as a "first in humans" randomized trial. "First in human" pharmaceutical trials focus upon safety. However because TP and fresh frozen plasma (FFP) are standards of care in PTr this proposed trial is somewhat different. While FFP/TP has a safe track record in the in-hospital treatment of the PTr victim and the trauma literature does show that early intervention with plasma has enhanced survival, its use in the prehospital setting demands a careful and deliberate approach centered on safety and the logistical preservation of the valuable resource of TP. This is a logical extension of the movement of a potentially valuable therapy in a time-critical injury to enhance a therapeutic window of opportunity.

The Blood Banking industry separates blood into components. FFP may be given as either type specific or universal donor. Uncross-matched plasma has been associated with increased adverse outcomes, but these data are not always in the context of limited use (2 units) as we are proposing for acute PTr in the prehospital setting.[58] Presently, it is the standard of care for patients presenting to combat care sites or civilian trauma centers to receive early and rapid use of FFP or TP without full cross match. As soon as cross match is available, and if matching units can be found, it is standard practice to use these matched products.

Blood products are a mainstay for civilian medicine with 14-16 million units collected/utilized per year. Allogeneic blood is therefore a precious resource. Trauma accounts for approximately 8-12% of the blood usage in the United States. If moving TP forward in treatment affects a savings in blood demand that would have great benefit on the blood supply as a whole. In the United States a 1.3-1.5 day supply of blood is on hand at any given time. Any decrease in blood demand would constitute a positive effect for homeland security.

If this trial shows efficacy in reducing mortality/morbidity, from the early forward use of TP, a significant advance for the civilian population will occur. Subsequent research studies will then be warranted to examine cost/benefit in generalizing the forward deployment of TP to prehospital care systems for the civilian population.

II. Exception from Informed Consent (EFIC):

This protocol will be submitted for IRB approval as Exception From Informed Consent (EFIC) in accordance with the so-called Final Rule, federal regulations 45 CFR 46 and 21 CFR 50.24. Participants will be enrolled in the study without consent with next of kin proxy consent obtained as soon as possible. VCU has conducted several EFIC trials and has in place a network of community consultants to support the effective, bi-directional information flow for the required Community Consultation and Public Notification. The researchers feel that this project fits exactly the criteria for such Exception From Informed Consent and are morally compelled (by medical literature, past history and present conflicts) to proceed. Adult patients of either sex, all races and ethnic origins (≥ 18 years of age) and not pregnant nor a prisoner will be eligible for enrollment. Clearly, PTr patients are likely to have altered consciousness and be unable to fully comprehend or give rational informed consent regarding a research protocol when first encountered in the field by paramedics. Patients entering the trial will fit inclusion/exclusion criteria and be randomized according to a randomization schedule. The EMS supervisor (Richmond Ambulance Authority-RAA or Henrico County Fire/EMS) will converge on scene of possible PTr candidates with TP and will determine if the victim fits criteria, radio the VCU

Medical Center (VCUMC) and speak with the attending physician on call for the study (trauma surgeon or ED attending physician). The direct verbal order will enroll the participant into the PUPTH trial.

III. Experience in Exception from Consent in Trauma Care Research at VCU:
Research conducted in any condition where time is critical to therapeutic efficacy and/or patients are not aware of their surroundings presents a challenging ethical dilemma. The FDA recognizes the critical importance of research on emergent conditions and does, under strict circumstances, allow an exception from informed consent.

In our region (greater Richmond, VA area) the transport time from site of injury to ED is 6-40 minutes (mean 26 minutes). We plan to utilize two of the 4 state of the art city and county EMS systems that serve the greater Richmond area. Together they serve a population of over 500,000. Additionally, VCUHS has significant experience in the preclinical and clinical testing of experimental blood products including the use of EFIC trials for the testing of a hemoglobin based oxygen carrier as well other prehospital emergency based EFIC trials that are part of the NIH sponsored Neurologic Emergency Treatment Trials network. The system also has great experience in the use of prehospital cold storage of saline having created a standard of providing intravenous 4° NS to victims of cardiac arrest for therapeutic hypothermia. Furthermore the system is heavily engaged in a wide-ranging array of combat casualty care research and training programs. These include but are not limited to platelet characterization in the victim of polytrauma, preclinical development and testing of spray dried plasma and oxygen carriers, and providing clinical training to half of the country's Special Operation Combat Medics. These and other factors make our system an ideal test bed for examining the use of prehospital plasma for traumatic hemorrhage.

IV. Consent IRB Issues:
VCU Institutional Review Board (IRB) approval of all protocols including informed consent procedures and community consultation and public notification strategies will be obtained prior to onset of subject enrollment. The planned study will use an Exception from Informed Consent (EFIC) in order to enroll acutely injured patients upon arrival. Every effort will be made to obtain full informed consent from the patient or legally authorized representative in all cases. However, in cases where consent is not possible subjects will be enrolled. For the subjects enrolled using EFIC, the subject and/or their legally authorized representatives who present after enrollment will be offered additional information and the opportunity to withdraw from the study if they wish.

Exception From Informed Consent is reasonable due to the following:

1) The research involved presents no more than minimal risk to subjects.
2) Subjects will likely receive TP soon after arrival at the trauma center- so that therapy is destined to happen.
3) The use of TP within the trauma center today is routine treatment, and is performed without informed consent in an emergency manner for trauma patients who would fit this study's entry criteria.
4) The waiver or alteration will not adversely affect the rights and welfare of the subjects.
5) The research cannot be practicably carried out without the waiver,
6) Subjects or their legally authorized representative will be provided additional information when the opportunity arises.
7) The Richmond community will have information regarding this study promoted as widely as possible with community meetings, and questions answered.

The intervention is also likely be of benefit to the participant; a required EFIC criteria. For reasons previously discussed the movement of TP to an earlier time point in the subjects care is likely to be of benefit.

The procedures used in this protocol are considered to expose subjects to non-significant risk since they may well receive TP anyway, later in the trauma center. We know that in many cases we will be unable to quickly locate a legally authorized representative (LAR). However, some of the most valuable information we hope to obtain from this study will be at the very early time points during resuscitation. Informed consent will be obtained from patients after their condition stabilizes or from their LAR in order to access the full medical record. The EFIC is justified on the grounds that the study will not pose more than minimal risk to patients. Legally authorized representatives will be identified as next of kin, durable power of attorney, or direct family relation. Consent will be obtained in person by signature. Every attempt will be made to obtain full informed consent from those patients who are judged to retain the capacity for proper understanding and judgment. Further daily attempts will also be made to obtain full informed consent from the patient directly or next of kin during their enrollment period in order to allow for them to opt out of further study participation. Subjects who regain the capacity for decision making who were enrolled initially through consent of a LAR will be re-consented. In order to maintain the integrity of the EFIC, blood draws will be limited to small infrequent volumes that will in no way impact the medical condition or course of the patient. The treating medical teams will also remain blinded to all study results so as to have no influence on medical decision making.

IV. Additional Protections

(i). We will conduct community consultation prior to starting the clinical trial.

(ii). We will provide public notification of the study (including information on the risks and expected benefits), before and during the clinical trial.

(iii). We will provide disclosure to the public of the results (including demographic characteristics of the study subjects) after completion of the study.

(iv). We will continue our efforts to find next of kin if EFIC is instituted. All of these efforts will be summarized for each patient.

(v). Records will be maintained for 5 years past study closure (per VCU requirements).

(vi). Specially protected populations (e.g. prisoners, fetuses, pregnant women, children) will not be included in the study.

V. Community Consultation:

In general, community consultation which will be conducted in the City of Richmond and County of Henrico will include: presentation of the details of the proposed clinical trial provided by one of the investigators, a question & answering session, and a survey of understanding. Free-standing, self-explanatory surveys will also be conducted which do not require a formal presentation to explain the proposed clinical trial and EFIC plan. A web site (go.VCU.edu/plasma), email address (plasmastudy@vcu.edu), and contact information (804-xxx-xxxx) will be available to the public for making comments and expressing any concerns. A record of all presentations, consultations, and survey results will be kept in order to provide a mechanism for community disclosure over the course of the clinical trial and after its conclusion.

More specifically, efforts to inform the entire greater Richmond community will be through print (newspapers, magazines, informational flyer and bus advertisements) and broadcast (radio ads, TV PSAs [public safety announcements]) as well as in radio and TV interviews. Information will be made available through religious groups and community leaders with targeted regions governed by the historical distribution of trauma victims. This approach could well concentrate information and outreach to housing projects, community sub-divisions (near intersections where blunt trauma was common) etc. Town, house of worship, and community meetings will be scheduled, publicized and held to explain the PUTHP trial and answer questions. At all of these meetings, and through phone

and email request lines any community member who wishes not to participate (opt out) of the PUPTH trial will have the opportunity to obtain a wrist band that clearly expresses their non-participation. Because of religious prohibitions, the researchers will contact the Jehovah's Witness Liaison committee (leadership). Their advice and contacts will be sought to get information (opt-out bands) to members of their congregations who wish not to participate. Any other ethnic, religious or community group brought to the attention of the research group will receive appropriate information and have an opportunity to ask questions.

The Community Engagement Core of the VCU Center for Clinical and Translational Research (CCTR) inaugurated a community partnership approach to Community Consultation and Public Disclosure for an Exception From Informed Consent (EFIC) trial, (RAMPART). Community partners as part of CARs (Community Advocates for Research) were chosen with established communication venues with target audiences, an essential element in bi-directional communication. Since then, the community advocates assisted with communication in another EFIC trial at VCU, dramatically decreasing research team man hours, cost, and time to completion, as well as increasing dissemination of information as ascertained by convenience sample surveys. This infrastructure will be made available to the VCURES team for the EFIC required Community Consultation and Public Notification. VCUMC, the Richmond Ambulance Authority and the Henrico County Fire and EMS service have experience in this challenging area as they have participated in the trial of public access of automated defibrillators, the Northfield Polyheme trial of pre-hospital provision of a hemoglobin based oxygen carriers as well as in the NIH's Neurologic Emergency Treatment Trials Network which has trialed pre-hospital use of midazolam autoinjection for status epilepticus and is trialing the use of intravenous progesterone for traumatic brain injury.

It has been the experience of VCU researchers involved with at least three other EFIC studies that scheduling independent meetings outside of the VCU and EMS communities has been poorly attended (i.e. only one or two community members). However, "piggy-backing" onto meetings already scheduled by different community organizations in the target area has had significantly larger audiences. Therefore, we feel that is the approach for the PUPTH study. CARs will be a good resource for identifying which meetings on which to be on the agenda.

Per DoD, wherever possible (unless insufficient space or time – e.g. on Twitter), US Army sponsorship of this research must be provided to the public.

Community presentations and surveys (participatory):
The following are the groups to which we propose to conduct a community consultation to begin approximately 6-8 weeks following approval of this phase. The IRB will be notified of dates and times of all scheduled presentations. When possible, members of the audience will be asked to complete a survey after the presentations.

- Working with the VCU Center for Clinical and Translational Research – specifically through their Campus Community Leadership Team (CCLT) and Community Advocates for Research (CARs) – we will fine-tune our list to be more specific to the groups they recommend and send speakers to those meetings.
- Richmond City Council Meeting – During the citizen comment period
- Richmond Health, Human Services, and Education Standing Sub-Committee Meeting – During the citizen comment period
- Henrico County Board of Supervisors – During the citizen comment period
- Meeting of the EMS organizations in Richmond and Henrico where leadership and members will be invited to attend
- Visitors to the VCU Medical Center who reside in the City of Richmond or Henrico County will be asked to complete the self-explanatory survey

APPROVED
JH /IR /4-11-13

- E-mail distribution of the self-explanatory survey to MCV Health System employees as well as all VCU faculty, staff and students
- A seminar presentation on the PUPTH clinical trial at a Grand Rounds or similar forum(s) at the MCV Health System

Community Announcements and advertisements

- E-mail distribution of flyer to MCV Health System employees as well as all VCU faculty and VCU students
- Announcement on VCU electronic signage throughout the university.
- E-mail distribution of the flyer-poster to faculty and students of The University of Richmond, Virginia Union University, and J. Sergeant Reynolds Community College
- Flyers in patient waiting rooms of the MCV Health System hospitals and clinics
- Presentation on a local TV talk show and/or local public radio in time allowed
- Press releases in the Richmond Times Dispatch, local community papers and newsletters as well as on public radio and TV
- Advertisements in weekly community periodicals and newspapers
- Bus sign will appear for at least a month in buses running in Richmond & Henrico
- Article about the PUPTH trial in a newsletter, weekly community periodical, and/or newspaper
- Website for PUPTH (www.go.vcu.edu/plasma) will be noted in all print and broadcast communications
- Social media sites including Facebook and Twitter will have entries.

Public Disclosure to communities prior to initiation of the study:

The community must also be informed before the trial commences about the trial, its design, risks and benefits. Based on other EFIC trials conduced at VCU, we will use similar methods to those studies, e.g. newspaper notification, public radio, websites, fliers, and informational flyers in Emergency Rooms.

Public disclosure at the completion of the trial:

After completion of the trial the public must be notified that the trial has ended, and given basic demographics of the research population and summary of results. As for the Public disclosure, we will follow those methods as other VCU investigators involved in EFIC trials and provide the public disclosure at the completion of the study be by newspaper articles and ads.

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Prehospital Use of Plasma for Traumatic Hemorrhage

(PUPTH Study)

Community Consultation

meeting location

Presented by: XXXXXX XXX, MD

MM/DD/YYYY

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Clinical Investigators

Principal Investigator
Bruce D Spiess, MD
Professor, VCU Department of Anesthesiology
Researcher VCU Reanimation Engineering Science Center (VCURES)

Sub-Investigators

- Michel Aboutanos, MD
- Donald Brophy, PharmD, MSc
- Therèse M Duane, MD
- Stephanie Goldberg, MD
- Michael C Kurz, MD
- Julie Mayglothling, MD
- Susan D Roseff, MD
- Jacob Wegelin, MD
- Brandon Wills, DO, MS
- Rahul Anand, MD
- Harinder Dhindsa, MD
- Paula Ferrada, MD
- Christopher Hogan, MD
- Ajai Malhotra, MD
- Joseph P Ornato, MD
- Kimberly W Sanford, MD
- James F Whelan, MD

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Study Sponsor

Funded by a grant from the

U.S. Army

Medical Research and Material Command

Combat Casualty Care Research Program

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Study Purpose

To see if patients who receive plasma as soon as possible after suffering a non-head related trauma have...

- Less
  - Bleeding
  - Need for additional blood
  - Pain
- Better clinical outcomes
- Improved survival rates

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Need for Improved Outcome

- The Center for Disease Control (CDC) lists trauma as the leading cause of death among Americans under age 45
- Uncontrolled bleeding is the leading cause of death from trauma
- Thousands of trauma patients die each year
- Many of these patients die because the "standard of care" cannot reverse the damage from too much blood loss

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What is the Standard of Care?

Represents the current treatment

At the Site of Injury or In the Ambulance	*In the Hospital*
The patient receives salt water	The patient receives salt water and donated parts of blood

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Standard of Care Limitations

At the Site of Injury or In the Ambulance

- Salt water does not carry blood or its parts such as plasma (part of the blood that causes it to clot)
- Salt water can dilute the blood too much
- If there is too little or no plasma
  - Blood cannot clot which leads to more bleeding
  - Organs can stop working
  - Patient can bleed to death

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Standard of Care Limitations

In the Hospital

- Patients who receive more than 6 units of donated blood in the first 12 hours have an increased risk of organ failure
- Increased blood transfusions weaken patient's normal immune state

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Why Giving Plasma at the Site or In the Ambulance Could Help

To improve survival of severely injured and bleeding patients

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Experience of Giving Plasma Early

- Plasma has been shown in pre-clinical studies...
  - To be better than salt water or other solutions that help get blood to the body's organs
  - To nearly equal fresh whole blood in preventing excessive bleeding or total blood loss.
- Plasma has been shown to be safe in the hospital for victims of trauma
- Giving plasma early has improved survival
- Trauma accounts for approximately 8-12% of the blood usage in the United States. Giving plasma earlier in the treatment may reduce the demand for blood that would have great benefit on the blood supply as a whole.

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Trial Design: Before the Hospital

Severely injured trauma patients will be randomized to either one of two groups

Control
50% Receive salt water
(as needed to maintain blood pressure)

Test
50% Receive up to 2 units Plasma *plus* salt water
(as needed to maintain blood pressure)

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Trial Design: At the Hospital

Control
- Salt water for hydration
- Donated blood products including plasma per standard of care

Test
- Salt water for hydration
- Donated blood products including plasma per standard of care

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Who Would Be Included?

Patients at risk of dying who...

- Have sustained severe injuries
- Have lost a large amount of blood and have either
  - very low blood pressure or
  - low blood pressure and high heart rate
- Are at least 18 years old
- Are of either gender (male or female)

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Who Would Be Excluded?

- Anyone wearing an opt-out wrist band
- Any patient or next of kin (who understands) refusing participation
- Documented "Do Not Resuscitate Order"
- Patients known to be pregnant
- Prisoners
- Patients who cannot speak English or Spanish
- Patients who require CPR
- Patients for whom EMS cannot start an IV line
- Less than 18 years old (i.e. is a minor)
- Patients not expected to survive transport to VCUMC
- Patients who have penetrating brain injuries
- Patients not having low blood pressure or who are easily treated for low blood pressure
- Patients with known objections to blood transfusions

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What is Informed Consent?

A process by which patients make informed decisions about participating in research studies

- Traditionally required for all research studies
- Research studies compare 2 treatments (standard vs. investigational)
- Doctors or research staff describe each of these potential treatments
- Patients are informed of the potential risks and potential benefits associated with each of these treatments
- Patients choose whether to participate in the study

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What is Exception from Informed Consent?

Patients are enrolled in a research study without giving their informed consent

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How Can That Be?

A federal regulation (21 CFR 50.24), created in 1996, allows certain studies that meet the following criteria to use this exception

- ***Patients' lives must be at risk***
- Available treatments are not satisfactory
- Patients are unable to give consent
- Potential risks are reasonable
- Participation in the research could provide a direct benefit ***(increased survival)*** to the patient
- The research could not be practicably carried out without an exemption

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Consent Safeguards

- If possible, the patient or a legally authorized representative (LAR)/adult family member can refuse before the patient is enrolled in the study
- If refusal cannot be obtained before enrollment, frequent attempts will be made to contact the patient's LAR or adult family to describe the study
- *The patient, a legally authorized representative, or adult family members may decide to withdraw the patient at any time*

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Potential Benefits of Giving Plasma Early

- Giving plasma early may provide improved survival
- Giving plasma earlier in the treatment may reduce the demand for blood that would have great benefit on the blood supply as a whole
- Could be used as guide for military combat use

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Potential Risks of Giving Plasma Early

- Inflammation
- Other bleeding problems
- Unforeseen happenings

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Patient Protection

- The Institutional Review Board (IRB) is a group of medical, scientific, and nonscientific members of the community
  - Reviews all proposals for research on humans
  - Assures patient safety
  - Monitors community feedback
- The IRB and U.S. Food and Drug Administration (FDA) will decide whether or not to allow this hospital to participate in the PUPTH trial
- An independent data monitoring committee will oversee the trial
- The FDA will be kept informed of the trial's progress

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If We Participate...

- The results of the study will be revealed to the community after the trial has been completed
- Those who do not want to participate in the study can wear a special wrist band to exclude themselves (opt-out)

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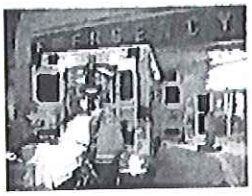

Questions
or
Comments?

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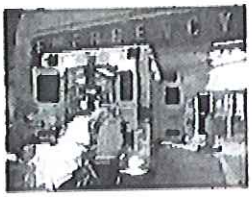

We would appreciate your completing a short survey.

Thank You

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Print ad
Community Consultation

(VCUHS LOGO)

VCU Plasma Study: Emergency Research

What YOU should know about participating in our clinical research without YOUR consent: If you have been hurt and are bleeding, you may get plasma before you arrive at the hospital.

Virginia Commonwealth University is proposing a research study to evaluate the use of thawed plasma (TM) by emergency services (EMS) before you reach the hospital. TM, a component of blood that helps it clot, is administered routinely in hospital for patients who have lost a lot of blood but it currently is not carried by EMS.

This study seeks to evaluate whether trauma patients who receive plasma earlier have improved survival rates.

Because of the severity of their injuries, **patients may not be able to provide consent**. Individuals who do not wish to participate may request an opt-out bracelet.

We encourage you to learn more about this study by visiting **go.vcu.edu/plasma** or calling **xxx-xxx-xxxx**.

Radio ad/psa
30-second
Community Consultation

General announcement

What **YOU** should know about participating in clinical research without **YOUR** consent: If you have been hurt and are bleeding, you may get plasma in the ambulance.

Virginia Commonwealth University is proposing a study to see if survival improves for patients who get thawed plasma by ambulance personnel before reaching the hospital. Plasma is administered routinely in hospital for those who have lost a lot of blood but is not carried by EMS.

Due to the severity of injuries, **patients may not be able to provide consent**. If you do not wish to participate you may request an opt-out bracelet.

We encourage you to learn more by visiting **go.vcu.edu/plasma** or calling **804-xxx-xxxx**.

Opt-out bracelet wording

I refuse the VCU plasma study

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Plasma Study
Website text
Go.vcu.edu/Plasma
Will "live" within the CCTR webpages (www.cctr.vcu.edu in Research Highlights section)

HOME:

VCU Plasma Study
Prehospital Use of Plasma for Traumatic Hemorrhage (PHPTH Study)

What YOU should know about participating in our clinical research without YOUR consent. If you have been hurt and are bleeding, you may get plasma BEFORE you arrive at the hospital.

Virginia Commonwealth University is proposing a research study to evaluate the use of thawed plasma (TP) by emergency services (EMS) before you reach the hospital. TP, a component of blood that helps it clot, is administered routinely in hospital for patients who have lost a lot of blood, but it currently is not carried by EMS.

Researchers want to investigate whether or not getting plasma as soon after a major trauma injury as possible can reduce bleeding/transfusion and pain and improve survival rates.

Read Plasma Study PowerPoint Presentation. (link to powerpoint slides 1-23)

In more than 95 percent of major trauma involving severe bleeding, patients receive blood products, including plasma, once they are transported to the hospital, usually immediately in the emergency department. Researchers want to know if giving plasma to non-head related trauma patients at the scene of the injury or in the ambulance on the way to the hospital improves health outcomes for the patients.

VCU is one of three academic medical centers in the country that has been selected to participate in this study, funded by a grant from the U.S. Army Medical Research and Material Command, Combat Casualty Care Research Program. VCU was selected to participate because of its Level I Trauma Center and the high number of trauma victims it receives.

Persons eligible for this study are at least 18 years old and non-pregnant. Because of the severity of their injuries, these individuals may not be able to provide consent to participate. Permission from the patient or their next of kin will be attempted as early as possible.

Individuals who do not wish to participate in this study may request an opt-out bracelet.

To request an opt-out bracelet:

Email plasmastudy@vcu.edu

Call 804-xxx-xxxx

Fill out the online form – click here (link to form – see form text below)

Links and Resources:

Opt-Out Form (see form text below)

General Informational Flier (link to pdf of general flier)

Potential Benefits of Giving Plasma Early (link to pdf slide 19)

Potential Risks of Giving Plasma Early (link to pdf slide 20)

Exception to Informed Consent (link to pdf slides 15-18)

Study PowerPoint Presentation (link to pdf of presentation, slides 1-23)

Clinical Investigators (link to pdf page of investigators)

Link to upcoming discussion meetings

Opt out online form (REDCap form):

I choose to ***NOT*** participate in VCU's Plasma study and would like to request a bracelet to wear while the study is active. It is anticipated that the study will continue through 2015.

Name:

Address:

City:

State:

Zip Code:

Phone Number (with area code):

Email:

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After hitting submit button, following text will appear:

Thank you for filling out the opt-out form for VCU's Plasma study. Someone from VCU will contact you to confirm your address prior to sending the bracelet to you. If you should have any questions, please call 804-xxx-xxxx or email plasmastudy@vcu.edu

Thank you.

VCU Digital Signs

Wordage:

VCU Plasma Study: Emergency Research

What YOU should know about participating in our clinical research without YOUR consent: If you have been hurt and are bleeding, you may get plasma (a component of blood) before you arrive at the hospital.

To learn more about this study, potential risks and benefits of treatment, as well as how to opt out, visit our website or call us.

go.vcu.edu/plasma
Or
804-xxx-xxxx

TelegRam and VCUHS mass mail posting

Investigators at the VCU Medical Center are proposing a research study (funded by US Army) to evaluate the use of thawed plasma (a component of blood) administered by EMS personnel to bleeding patients before they reach the hospital. Patients may not be able to give consent. Those who do not wish to participate can opt-out by requesting a bracelet that must be worn at the time of trauma. For more information, visit ***http://go.vcu.edu/plasma.***

GRTC Bus Signs for rear of bus (needs VCUMC logo)

Wordage:

VCU Plasma Study: Emergency Research

What YOU should know about participating in our clinical research without YOUR consent: If you have been hurt and are bleeding, you may get plasma (a component of blood) before you arrive at the hospital.

To learn more about this study, potential risks and benefits of treatment, as well as how to opt out, visit our website or call us.

go.vcu.edu/plasma
Or
804-xxx-xxxx

Broadcast Email

Virginia Commonwealth University plans to conduct a research study that could potentially save the lives of trauma patients. However, prior to getting final approval to participate in the study, the Institutional Review Board (IRB) requires that VCU to provide information within the community from which likely study participants will come, including Richmond and the County of Henrico.

For the widest possible audience to be informed, Principal Investigator Bruce Spiess, M.D., is respectfully requesting that you please read the following information and post the attached flier where appropriate for the public to see. In addition, please feel free to forward to anyone in your address book that lives, works or travels through either the City of Richmond or Henrico County.

If you have any questions, please email plasmastudy@vcu.edu.

****

VCU Plasma Study: Emergency Research Without Consent

Virginia Commonwealth University is proposing a research study (funded by the US Army) to evaluate the use of thawed plasma (TP) by emergency services (EMS) before patients reach the hospital. TP is a component of blood that helps it clot. While TM is administered routinely in the hospital for patients who have lost a lot of blood (are in shock), it currently is not carried by EMS personnel.

This study will evaluate whether patients who receive plasma by EMS personnel as soon as possible after suffering a major trauma have:

- reduced bleeding and pain,
- better clinical outcomes and
- improved survival rates.

Persons eligible for this study are at least 18 years old and non-pregnant. Because of the severity of their injuries and loss of blood, these individuals may not be able to provide consent to participate. Permission will be obtained from the patient or their next of kin as early as possible.

You can refuse to participate in the study by requesting an opt-out bracelet. The bracelet must be worn at all times so that EMS will know you do not wish to be in the study.

Once approved by the U.S. Food and Drug administration and the VCU Institutional Review Board, the study is expected to last for three years.

To learn more about this study, potential risks and benefits of treatment, as well as how to opt out, visit our website or call us.

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OFFICE OF RESEARCH
MAR 19 2013
SUBJECT PROTECTION

(For groups on which we piggy back meetings, etc)

Meeting announcement Email

Virginia Commonwealth University plans to conduct a research study (funded by the US Army) that could potentially save the lives of trauma patients. This study involves the use of plasma (a component of blood) for persons with severe trauma who may not be able to provide consent. Therefore, prior to getting final approval to participate in the study, the United States Food and Drug Administration and the VCU Institutional Review Board (IRB) require that VCU provide information within and seek comments from the community from which likely study participants will come, including Richmond and the County of Henrico.

The following public meetings are scheduled to provide more information about this study. Please print out the attached meeting announcement and post where appropriate and share this email with colleagues and friends who live, work or may be traveling through Richmond and/or Henrico. *Thank you.*

Public Meetings:
Date
Time
Place

Date
Time
Place

Date
Time
Place

If you have any questions, please email plasmastudy@vcu.edu.

For more information, visit go.VCU.edu/plasma.

(For groups on which we piggy back meetings, etc: wording only [not graphics layout])

Meeting announcement flier

Getting Plasma Sooner
Learn more about our research

Please plan to attend ONE of the following public meetings

Date
Time
Place

Date
Time
Place

Date
Time
Place

The public is invited to learn about VCU's proposed research study (funded by the US Army) to evaluate the use of thawed plasma (a component of blood) administered by emergency services (EMS) personnel before the patient reaches the hospital. Currently, the standard of care by EMS personnel at the scene of the trauma is to give patients saline (salt water) solution to keep blood pressure up until the patient reaches the hospital. Saline, however, does not carry the elements that allow blood to clot. The aim of this study is to evaluate whether patients who receive plasma as soon as possible after suffering a non-head related trauma have reduced bleeding and pain, better clinical outcomes and improved survival rates. Because of the severity of their injuries, the patients may be enrolled without their consent. XXXXXXX XXXXXX, title, will describe the study, potential risks and benefits and explain how the public may opt out of the study. This is an opportunity to listen, comment, and/or ask questions specific to the study.

For more information, contact xxxxxx xxxxxx, title
Phone: xxx-xxx-xxxx
Email: plasmastudy@vcu.edu
Web site: go.vcu.edu/plasma

General information flyer
Community Consultation

VCU Plasma Study: Emergency Research Without Consent

Virginia Commonwealth University is proposing a research study (funded by the US Army) to evaluate the use of thawed plasma (TP) by emergency services (EMS) before patients reach the hospital. TP is a component of blood that helps it clot. While TP is administered routinely in the hospital for patients who have lost a lot of blood (are in shock), it currently is not carried by EMS personnel.

This study will evaluate whether patients who receive plasma by EMS personnel as soon as possible after suffering a major trauma have:

- reduced bleeding and pain,
- better clinical outcomes and
- improved survival rates.

Persons eligible for this study are at least 18 years old and non-pregnant. Because of the severity of their injuries and loss of blood, these individuals may not be able to provide consent to participate. Permission will be obtained from the patient or their next of kin as early as possible.

You can refuse to participate in the study by requesting an opt-out bracelet. The bracelet must be worn at all times so that EMS will know you do not wish to be in the study.

Once approved by the Food and Drug Administration and the VCU Institutional Review Board, the study is expected to last for three years.

To learn more about this study, potential risks and benefits of treatment, as well as how to opt out, visit our website or call us.

go.vcu.edu/plasma
Or
804-xxx-xxxx

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Please **do not** place your name on this form

We would like to hear from you anonymously. We want to know about what you heard and find out what you think and how you feel about what we have shared with you today. There are no known risks involved in participating in this survey. Your participation in this survey is completely voluntary. You may refuse to participate, and not to answer any questions that you do need feel comfortable answering.

To start, five questions have been listed below related to the Plasma study information that was shown and talked about today. Your answers will help us improve how we present this information to others at future community events.

---

1. This study involves receiving a component of blood before reaching the hospital. What component is given? (Check only one)

__Platelets __Thawed plasma __White blood cells __ I don't know

2. In addition to standard medical care by EMS personnel for trauma patients, which one of the following statements below is true about what type of treatment patients will receive if they are enrolled in the Plasma study? (Check only one)

__ All patients in this study will receive plasma by EMS personnel before reaching the hospital

__ Patients in this study will receive EITHER salt water or plasma *and* salt water

__ I don't know

3. Which of the following are possible risks, or side effects, of receiving Plasma prior to the hospital? (Check all that apply)

__ Inflammation

__ Other bleeding problems

__ Hair growth

__ Seizures

__ I don't know

4. Which of the following statements are true about the Plasma study? (Check all that apply)

__ Some patients who receive plasma before the hospital might have reduced bleeding

__ No patient in this study will benefit directly

__ Some patients who receive plasma before the hospital might have better outcomes

__ I don't know

5. Not all trauma patients included in the Plasma study will be given plasma by EMS personnel. How is it decided which treatment patients receive? (Check only one)

__ Study doctors choose which patients receive the plasma before the hospital.

__ It is decided at random, like in a coin toss.

__ I don't know

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Please **do not** place your name on this form

Next, we would like to know your feelings and opinions about the Plasma study. Please tell us how much you agree with each of the following six statements.

	Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree
6. The Plasma study is an important study to do.					
7. After hearing about the possible benefits and risks of the Plasma study, you believe that it is acceptable to test getting plasma before the hospital in trauma injury patients.					
8. Sometimes no family member can be found to make medical decisions for patients with severe trauma injury. It is okay to include those patients in the Plasma study without consent.					
9. If you had a major trauma injury and no family member could be found to make decisions for you, you would be okay with being included in the Plasma study without consent.					
10. If you had a trauma injury and a family member agreed to include you in the Plasma study, you would be okay with being included.					

11. Do you think that the Plasma study researchers will seriously consider what community members like you have to say about this study before starting it?

__ Yes __ No __ I Don't know

12. Do you feel that you have been given enough information to give your informed opinion about whether you think it is ok for researchers to do the Plasma study?

__ Yes __ No

12a. If you answered No, to question 12 above, what information would you still like to know?

_____

_____

13. Have you or has anyone you know ever experienced a trauma injury? (Check all that apply)

__ Me __ A family member or loved one __ Someone else I know __ No

14. A wrist band is available ahead of time that you can wear to tell doctors that you DO NOT want to participate in this study. The wrist band says "I refuse the VCU Plasma Study." EMS personnel will not include eligible trauma patients wearing these wrist bands in the Plasma study. Do you want to wear one of these wrist bands?

__ Yes (Pick up a Plasma informational sheet and contact the study team listed to get a wrist band sent to you)

__ No

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14a. Can you tell us why you do or else do not want to wear a wrist band?

_____

Lastly, so that we can make sure we are hearing from a wide range of Richmond and Henrico residents, please complete the following final seven questions about yourself.

15. What is your age group?

__ Age 17 years old or younger
__18-24 years old
__25-34 years old
__35-44 years old
__45-S4 years old
__55-64 years old
__45-54 years old
__55-64 years old
__ Age 65+

16. Are you: __ Male __ Female

17. Are you Hispanic or Latino? __ Yes __ No __ I don't know

18. Which one or more of the following would you say is your race: (Check all that apply)

__White
__Black or African American
__Asian
__Native Hawaiian or Other Pacific Islander
__American Indian or Alaska Native
__Other [specify]_____

19. Where do you live? __ City of Richmond __ Henrico County __ Other

20. What is the highest grade or year of school you completed?

__ Never attended school or only attended kindergarten
__ Grades 1 through 8 (Elementary)
__ Grades 9 through 11 (Some high school)
__ Grade 12 or GED (High school graduate)
__ College 1 year to 3 years (Some college or technical school)
__ College 4 years or more (College graduate)

21. Please provide below, any additional comments, concerns or questions you would like to share with the Plasma study team:

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Please **do not** place your name on this form

This study is being funded by the United States Army.

Be sure to ask for a copy of the Plasma research team's contact information on your way out if you would like to contact them further.

Return this survey to a study team member ***Thank You!***

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Please do not place your name on this form

VCU Medical Center researchers are planning to conduct a plasma study funded by the US Army. This study may affect you or someone you know and we need to find out ahead of time what the residents of Richmond and Henrico County think about it. THANK YOU for your help and time in completing this survey.

There are no known risks involved in participating in this survey. Your participation in this survey is completely voluntary. You may refuse to participate, and not to answer any questions that you do need feel comfortable answering.

1. Have you ever participated in a medical research study? __ Yes __ No
2. Have you ever given permission or signed a consent form for someone else to participate in a research study? __ Yes __ No

VCU Plasma Study: Emergency Research

The VCU Plasma study wants to evaluate the use of thawed plasma (TP) by emergency services (EMS) before patients reach the hospital. TP is a component of blood that helps it clot. While TP is given routinely in the hospital for patients who have lost a lot of blood, it is currently not carried by EMS personnel.

Potential risks of getting plasma early include inflammation and/or other bleeding problems. There may be other risks not known at this time, but all study patients will be carefully monitored while they are being treated for side effects. Patients will be notified if new side effects are discovered that affect their risk of being included in the study. There are several potential benefits to trauma patients who receive plasma earlier. These benefits may include improved survival, reduced need for blood, less pain and better outcomes.

3. This study involves receiving a component of blood before reaching the hospital. What component is given? (Check only one)

__ Platelets __ Thawed plasma __White blood cells __ I don't know

4. Which of the following are possible risks, or side effects, of receiving plasma early? (Check all that apply)

__ Inflammation
__ Other bleeding problems
__ Hair growth
__ Seizures
__ I don't know

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5. Which of the following statements are true about the Plasma study? (Check all that apply)

__ Some patients who receive plasma before the hospital might have reduced bleeding

__ No Patient in this study will benefit directly

__ Some patients who receive plasma before the hospital might have better outcomes.

__I don't know

How the Plasma Study Will be Conducted

Identifying patients who are eligible for the study

Severely injured trauma patients will be enrolled in either one of two groups. One group, called the Control Group, will receive salt water (saline solution), by EMS personnel. This is the current standard of care. The other group, called the Test Group, will receive up to two units of thawed plasma (TP) plus salt water (saline solution).

Only adults (i.e. at least 18 years of age) who are not pregnant, who have sustained severe injuries, lost a large amount of blood and have very low blood pressure or low blood pressure and a high heart rate are eligible for the Plasma study.

How the Plasma Study is different from other research studies

Obtaining medical consent for the research study

Once a patient is identified by trained Emergency Services (EMS) personnel as being eligible for the Plasma study, the EMS will attempt to locate a family member. Once found, the EMS supervisor will attempt to let the family know about the study and ask for their consent. Because plasma must be started quickly, if a family member is not located, the trauma patient may be enrolled in the Plasma study without consent.

However, at the hospital, as soon as a family member can be found or the patient becomes awake, whichever comes first, a member of the research team will speak to them. They will then be told about the research study including what has happened so far and asked if they want to continue. If they decide to continue participating, they will be asked to sign a consent form.

Study protocol and procedures

Study patients will be given saline and TP if EMS supervisors are carrying TP in special refrigerators in their vehicle at the time of arrival to the site of injury. All other study patients will be given only saline. Half of the patients will receive standard medical care for their trauma injury in the ambulance on the way to the hospital. This standard of care is saline solution, or salt water, given intravenously as needed to maintain blood pressure. The other half will receive an intravenous infusion of thawed plasma, which is referred to as the study treatment, *plus* salt water. Once the patients reach the hospital, all will receive the standard of care. In more than 95% of all major trauma involving severe bleeding, patients receive blood products, including plasma, once they arrive at the hospital.

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7. In addition to standard medical care for trauma injury, which one of the following statements below is true about what type of treatment patients will receive if they are enrolled in the plasma study? (Check only one)

__ All patients in this study will be treated with plasma in the ambulance on the way to the hospital.

__ Patients in this study will be treated with **EITHER** an IV infusion of salt water **OR** an IV infusion of salt water and thawed plasma.

__ I don't know

8. Not all patients included in the plasma study will be treated with thawed plasma before they reach the hospital. How is it decided which treatment patients receive? (Check only one)

__ Study doctors choose which patients need the study medication.

__ It is decided at random, like in a coin toss.

__ It is determined by whether or not the EMS supervisor is carrying thawed plasma

__ I don't know

Next, we would like to know your feelings and opinions about the plasma study. Please tell us how much you agree with each of the following six statements.

	Strongly Agree	**Agree**	**Neutral**	**Disagree**	**Strongly Disagree**
9. The Plasma study is an important study to do.					
10. After hearing about the possible benefits and risks of the Plasma study, you believe it is acceptable to test getting plasma before the hospital in trauma injury patients.					
11. Sometimes no family member can be found to make medical decisions for patients with major trauma injury. It is okay to include those patients in the Plasma study without consent.					
12. If you had a major trauma injury and no family member could be found to make decisions for you, you would be okay with being included in the Plasma study without consent.					
13. If you had a major trauma injury and a family member agreed to include you in the Plasma study, you would be okay with being included.					

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14. Do you think that Plasma study researchers will seriously consider what community members like you have to say about this study before starting it?

__Yes __No __I don't know

15. Do you feel that you have been given enough information to give your informed opinion about whether you think it is ok for researchers to do the Plasma study?

__Yes __No

15a. If you answered No, to question 15 above, what information would you still like to know?

_____

_____

16. A wrist band is available ahead of time that you can wear to tell doctors that you DO NOT want to participate in this study. The wrist band says "I refuse the VCU Plasma Study." EMS personnel will not include eligible trauma injury patients wearing these wrist bands in the Plasma study. Do you want to wear one of these wrist bands?

__ Yes (Pick up a Plasma informational sheet and contact the study team listed to get a wrist band sent to you)

__ No

16a. Can you tell us why you do/do not want to wear a wrist band?

_____

_____

Lastly, so that we can make sure we are hearing from a wide range of residents in Richmond and Henrico, please complete the following final seven questions about yourself.

17. What is your group?

__Age 17 years old or younger

__18 – 24 years old

__25 - 34 years old

__35 - 44 years old

__45 - 54 years old

__55 - 64 years old

__65 + years old

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18. Are you: __ Male __ Female

19. Are you Hispanic or Latino? __ Yes __ No __ I don't know

20. Which one or more of the following would you say is your race: (Check all that apply)

__ White or Caucasian

__ Black or African American

__ Asian

__ Native Hawaiian or Other Pacific Islander

__ American Indian or Alaska Native

__ Other [specify]_____

21. Where do you live?

__ City of Richmond __ Henrico County __ Other

22. What is the highest grade or year of school you completed?

__ Never attended school or only attended kindergarten

__ Grades 1 through 8 (Elementary)

__ Grades 9 through 11 (Some high school)

__ Grade 12 or GED (High school graduate)

__ College 1 year to 3 years (Some college or technical school)

__ College 4 years or more (College graduate)

23. Please provide any additional comments below or on the back of this page, concerns or questions you would like to share with the Plasma study team:

Be sure to ask for a copy of the Plasma research team's contact information if you would like to contact them further.

This study is being funded by the US Army.

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Thank you, this concludes this survey!

Please return your completed survey to a study team member.

Social Media

Facebook
Account: VCU Center for Clinical and Translational Research
http://www.facebook.com/VCU.CCTR

Facebook ad
Budget: $100/week for 2 weeks = total $200
Total reach: 759,440

Target:
People who live in Virginia
Age 18 and older
Are in one of the categories: Health & Wellbeing, education/teaching or News
Reach: 759,440
$1.25 per click (limit $100 week)
Ad to steer people of facebook post on VCU Clinical and Translational Research facebook page (see post #1 below)

Posts:
1) Press Release (see plasma grant_release)
Tag: Proposed VCU study to evaluate early intervention using plasma administered by EMS personnel to trauma patients.

2) Visit go.vcu.edu/plasma for more information on an important research study proposed by VCU. Study will evaluate if getting plasma sooner improves survival rates of major trauma patients.

Post and Calendar entry:
3) Join us for an upcoming public meeting about VCU's proposed plasma research study. You are invited to attend an open meeting to learn more about the study, its potential risks and benefits and how to opt out of the study.
Date, Time and Place
For more information, go to http://go.vcu.edu/plasma

Twitter
Account: VCUMedResearch
https://twitter.com/vcumedresearch

Tweets:
1) VCU proposes research study to evaluate early intervention using plasma in trauma patients http://go.vcu.edu/plasma #optoutstudy #research #VCU

2) Richmond & Henrico Co. residents: learn more about plasma study involving trauma injuries. #optoutstudy http://go.vcu.edu/plasma #research #VCU

3) Getting plasma sooner without your consent. Learn about plasma research study through VCU #optoutstudy http://go.vcu.edu/plasma #research #VCU

4) Learn about #VCU plasma research study, risks, benefits & how to opt out at public meeting. For more info: http://go.vcu.edu/plasma #optoutstudy

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Date

Name
Address
City, State zip

Dear Mr/Ms Name:

This is in response to your recent request to opt out of the plasma study. Included with this
is/are the wrist band/s bearing the words "I Refuse the VCU Plasma Study" that you requested.

Please keep in mind that **this band must be worn on your wrist** in the event that you are involved in a trauma situation and you do not want the emergency medical personnel to enroll you into the trial. They have been trained to look on your wrist for this band and **if you are wearing it**, they know that you will **not** be a study participant (i.e. you will receive salt water which is the current standard of care).

This study is expected to last from Month, yyyy – month, yyyy

If you have any questions about the study, please feel free to contact me. I can be reached via:

- Email: plasmastudy@vcu.edu or
- Phone: 804-xxx-xxxx or
- Website: www.go.vcu.edu/plasma

Thank you.

Sincerely,

Judy Katzen, RN, MS
Study Coordinator

This study is funded by the US Army

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PUPTH Grant PAID Marketing Plan: Community Consultation Phase

Appendix 18 — 8/29/2012

Print Media	**Frequency**
Richmond Times Dispatch (daily)	2x (1 on Sunday and 1 on Wednesday) Size: 4.89" x 5.25"; black and white
Style Weekly (weekly)	2x Size: 4.4" x 5.3"; black and white
The Voice (weekly)	2x Size: 5" x 5"; black and white
Richmond Free Press (weekly)	2x Size 5.418" x 5"; black and white
Henrico Citizen (2/month)	2x Size: 4.75" x 6"; black and white
Radio	
Cox: K95 (country) Hot 100.9 (today's hits)	approx. 30 spots (30 sec) for one week, split between the two stations
Clear Channel: 106.5 The Beat (hip hop, urban)	approx. 30 spots (30 sec) for one week
NPR	2 week campaign
GRTC Bus Signs	5 "buses"* at $210/per Queen size, rear of bus *buses: Per GRTC procedure IN which buses are randomly assigned routes each morning, there is no way to specify desired routes or particular buses; buses change out throughout the day which should provide community notification throughout the area
Website	Creative Services to create page
Within the CCTR site, url to use go.vcu go.vcu.edu/plasma	$100/hour; estimating 5 hours
Social Media	
Facebook ad	$100/week; for 2-3 weeks based on click-throughs from ad to website and/or post
General Flier	2000 flyers

Use the following table to document attempts to contact subject / LAR / family.

Patient ID Number / Initials	SC Initials/ date/time	Comments		SC Initials/ date/time	Comments		SC Initials/ date/time	Comments
Scene EMS Arrival Date and Time *(Time of Injury)*			9th Attempt Notification Date and Time (twice daily)			19th Attempt Notification Date and Time (twice daily)		
ED EMS Arrival Date and Time *(Clock Starts)*			10th Attempt Notification Date and Time (twice daily)			20th Attempt Notification Date and Time (weekly)		
1st SC Attempt Notification Date and Time			11th Attempt Notification Date and Time (twice daily)			20th Attempt Notification Date and Time (weekly)		
2nd SC Attempt Notification Date and Time (30 min)			12th Attempt Notification Date and Time (twice daily)			20th Attempt Notification Date and Time (weekly)		
3rd SC Attempt Notification Date and Time (60 min)			13th Attempt Notification Date and Time (twice daily)			20th Attempt Notification Date and Time (weekly)		
4th SC Attempt Notification Date and Time (120 min)			14th Attempt Notification Date and Time (twice daily)			20th Attempt Notification Date and Time (weekly)		
5th Attempt Notification Date and Time (1st within remainder of 1st 24 hours)			15th Attempt Notification Date and Time (twice daily)			20th Attempt Notification Date and Time (weekly)		
6th Attempt Notification Date and Time (2nd within remainder of 1st 24 hours)			16th Attempt Notification Date and Time (twice daily)					
7th Attempt Notification Date and Time (3rd within remainder of 1st 24 hours)			17th Attempt Notification Date and Time (twice daily)					
8th Attempt Notification Date and Time (twice daily)			18th Attempt Notification Date and Time (twice daily)					

Explain when signature(s) was obtained on consent form by patient, LAR (relationship) and/or Family Member (relationship). Include date(s) and time(s).

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Appendix 23
Eliciting Refusal Script

(Patient) has lost a lot of blood which can be very dangerous. Besides the salt water being given to try to raise blood pressure and stop the bleeding, we are looking at giving plasma, a part of blood usually given at the hospital. We are participating in an approved emergency research project to see how helpful giving plasma now is compared to just salt water. You will learn more about this at the hospital. If you do not object, we will start the plasma by IV right away and will then take (him/her) to the VCU Health Systems.

APPENDIX 2

VIRGINIA COMMONWEALTH UNIVERSITY

VCU

Make it real.

Office of Research Subjects Protection
Bio-Tech Research Park, Building 1
800 E. Leigh St., Ste.#3000
P.O. Box 980568
Richmond, Virginia 23298-0568

DATE: May 28, 2013

TO: Bruce Spiess, MD
Anesthesiology

FROM: Andrea Hastillo, MD
Chairperson, VCU IRB Panel C
Box 980568

Andrea Hastillo MD
May 30 2013

RE: **VCU IRB #: HM14813**
Title: Pre-Hospital Use of Plasma for Traumatic Hemorrhage (PHUPTH)

The following ***change(s)*** to your research study involving the research use of human subjects were ***approved for community consultation*** by the VCU IRB on May 23, 2013 according to 21 CFR 50.24. The approval is for community consultation activities only.

This community consultation approval includes the following items reviewed by this Panel:

- Prehospital Use of Plasma for Traumatic Hemorrhage (PUPTH Study) Community Consultation PowerPoint Presentation – Version Date 5/13/13-stamped received 5/10/13
- Appendix 4: Plasma Study Website text: Go.vcu.edu/Plasma, Version Date 5/9/13-stamped received 5/10/13
- VCU IRB Study Personnel Roster, Version Date 5.9.2013-stamped received 5/10/13

IMPORTANT NOTES:

- The IRB must be notified of the date and time established for community consultation meetings. Transcriptions/minutes must be made of all the community consultation meetings and submitted to the panel for review.

If you have any questions, please contact Dr. Andrea Hastillo, Chairperson, VCU IRB Panel C, at ahastillo@mcvh-vcu.edu or 301-7698; or you may contact Ingrid Rosiuta, IRB Coordinator, VCU Office of Research Subjects Protection, at IRBPanelC@vcu.edu or 827-1446.

Prehospital Use of Plasma for Traumatic Hemorrhage

(PUPTH Study)

Community Consultation

meeting location

Presented by: XXXXXX XXX, MD

MM/DD/YYYY

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Clinical Investigators

Principal Investigator
Bruce D Spiess, MD
Professor, VCU Department of Anesthesiology
Researcher VCU Reanimation Engineering Science Center (VCURES)

Sub-Investigators

- Michel Aboutanos, MD
- Donald Brophy, PharmD, MSc
- Therèse M Duane, MD
- Stephanie Goldberg, MD
- Michael C Kurz, MD
- Julie Mayglothling, MD
- Susan D Roseff, MD
- Jacob Wegelin, PhD
- Brandon Wills, DO, MS
- Rahul Anand, MD
- Harinder Dhindsa, MD
- Paula Ferrada, MD
- Christopher Hogan, MD
- Ajai Malhotra, MD
- Joseph P Ornato, MD
- Kimberly W Sanford, MD
- James F Whelan, MD

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Study Sponsor

Funded by a grant from the
U.S. Army
Medical Research and Material Command
Combat Casualty Care Research Program

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Study Purpose

To see if patients who receive plasma as soon as possible after suffering a non-head related trauma have...

- Less
  - Bleeding
  - Need for additional blood
  - Pain
- Better clinical outcomes
- Improved survival rates

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Need for Improved Outcome

- The Center for Disease Control (CDC) lists trauma as the leading cause of death among Americans under age 45
- Uncontrolled bleeding is the leading cause of death from trauma
- Thousands of trauma patients die each year
- Many of these patients die because the "standard of care" cannot reverse the damage from too much blood loss

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What is the Standard of Care?

Represents the current treatment

At the Site of Injury or In the Ambulance	*In the Hospital*
The patient receives salt water	The patient receives salt water and donated parts of blood

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OFFICE OF RESEARCH
MAY 10 2013
SUBJECT PROTECTION

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Standard of Care Limitations

At the Site of Injury or In the Ambulance

- Salt water does not carry blood or its parts such as plasma (part of the blood that causes it to clot)
- Salt water can dilute the blood too much
- If there is too little or no plasma
  - Blood cannot clot which leads to more bleeding
  - Organs can stop working
  - Patient can bleed to death

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Standard of Care Limitations

In the Hospital

- Patients who receive more than 6 units of donated blood in the first 12 hours have an increased risk of organ failure
- Increased blood transfusions weaken patient's normal immune state

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Why Giving Plasma at the Site or In the Ambulance Could Help

To improve survival of severely injured and bleeding patients

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Experience of Giving Plasma Early

- Plasma has been shown in pre-clinical studies...
  - To be better than salt water or other solutions that help get blood to the body's organs
  - To nearly equal fresh whole blood in preventing excessive bleeding or total blood loss.
- Plasma has been shown to be safe in the hospital for victims of trauma
- Giving plasma early has improved survival
- Trauma accounts for approximately 8-12% of the blood usage in the United States. Giving plasma earlier in the treatment may reduce the demand for blood that would have great benefit on the blood supply as a whole.

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Trial Design: Before the Hospital

Severely injured trauma patients will be randomized to either one of two groups

Control
50% Receive salt water
(as needed to maintain blood pressure)

Test
50% Receive up to 2 units Plasma *plus* salt water
(as needed to maintain blood pressure)

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Trial Design: At the Hospital

Control

- Salt water for hydration
- Donated blood products including plasma per standard of care

Test

- Salt water for hydration
- Donated blood products including plasma per standard of care

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Who Would Be Included?

Patients at risk of dying who...

- Have sustained severe injuries
- Have lost a large amount of blood and have either
  - very low blood pressure or
  - low blood pressure and high heart rate
- Are at least 18 years old
- Are of either gender (male or female)

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Who Would Be Excluded?

- Anyone wearing an opt-out wrist band
- Any patient or next of kin (who understands) refusing participation
- Documented "Do Not Resuscitate Order"
- Patients known to be pregnant
- Prisoners
- Patients who cannot speak English or Spanish
- Patients who require CPR
- Patients for whom EMS cannot start an IV line

- Less than 18 years old (i.e. is a minor)
- Patients not expected to survive transport to VCUMC
- Patients who have penetrating brain injuries
- Patients not having low blood pressure or who are easily treated for low blood pressure
- Patients with known objections to blood transfusions

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What is Informed Consent?

A process by which patients make informed decisions about participating in research studies

- Traditionally required for all research studies
- Research studies compare 2 treatments (standard vs. investigational)
- Doctors or research staff describe each of these potential treatments
- Patients are informed of the potential risks and potential benefits associated with each of these treatments
- Patients choose whether to participate in the study

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What is Exception from Informed Consent?

Patients are enrolled in a research study without giving their informed consent

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How Can That Be?

A federal regulation (21 CFR 50.24), created in 1996, allows certain studies that meet the following criteria to use this exception

- ***Patients' lives must be at risk***
- Available treatments are not satisfactory
- Patients are unable to give consent
- Potential risks are reasonable
- Participation in the research could provide a direct benefit ***(increased survival)*** to the patient
- The research could not be practicably carried out without an exemption

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Consent Safeguards

- If possible, the patient or a legally authorized representative (LAR)/adult family member can refuse before the patient is enrolled in the study
- If refusal cannot be obtained before enrollment, frequent attempts will be made to contact the patient's LAR or adult family to describe the study
- *The patient, a legally authorized representative, or adult family members may decide to withdraw the patient at any time*

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Potential Benefits of Giving Plasma Early

- Giving plasma early may provide improved survival
- Giving plasma earlier in the treatment may reduce the demand for blood that would have great benefit on the blood supply as a whole
- Could be used as guide for military combat use

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Potential Risks of Giving Plasma Early

- Inflammation
- Other bleeding problems
- Unforeseen happenings

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Patient Protection

- The Institutional Review Board (IRB) is a group of medical, scientific, and nonscientific members of the community
  - Reviews all proposals for research on humans
  - Assures patient safety
  - Monitors community feedback
- The IRB and U.S. Food and Drug Administration (FDA) will decide whether or not to allow this hospital to participate in the PUPTH trial
- An independent data monitoring committee will oversee the trial
- The FDA will be kept informed of the trial's progress

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If We Participate...

- The results of the study will be revealed to the community after the trial has been completed
- Those who do not want to participate in the study can wear a special wrist band to exclude themselves (opt-out)

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Questions
or
Comments?

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We would appreciate your completing a short survey.

Thank You

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Plasma Study
Website text
Go.vcu.edu/Plasma
Will "live" within the CCTR webpages (www.cctr.vcu.edu in Research Highlights section)

HOME:

VCU Plasma Study
Prehospital Use of Plasma for Traumatic Hemorrhage (PHPTH Study)

What YOU should know about participating in our clinical research without YOUR consent. If you have been hurt and are bleeding, you may get plasma BEFORE you arrive at the hospital.

Virginia Commonwealth University is proposing a research study to evaluate the use of thawed plasma (TP) by emergency services (EMS) before you reach the hospital. TP, a component of blood that helps it clot, is administered routinely in hospital for patients who have lost a lot of blood, but it currently is not carried by EMS.

Researchers want to investigate whether or not getting plasma as soon after a major trauma injury as possible can reduce bleeding/transfusion and pain and improve survival rates.

Read Plasma Study PowerPoint Presentation. (link to powerpoint slides 1-23)

In more than 95 percent of major trauma involving severe bleeding, patients receive blood products, including plasma, once they are transported to the hospital, usually immediately in the emergency department. Researchers want to know if giving plasma to non-head related trauma patients at the scene of the injury or in the ambulance on the way to the hospital improves health outcomes for the patients.

VCU is one of three academic medical centers in the country that has been selected to participate in this study, funded by a grant from the U.S. Army Medical Research and Material Command, Combat Casualty Care Research Program. VCU was selected to participate because of its Level I Trauma Center and the high number of trauma victims it receives.

Persons eligible for this study are at least 18 years old and non-pregnant. Because of the severity of their injuries, these individuals may not be able to provide consent to participate. Permission from the patient or their next of kin will be attempted as early as possible.

Individuals who do not wish to participate in this study may request an opt-out bracelet.

To request an opt-out bracelet:

Email plasmastudy@vcu.edu

Call 804-82-PLASMA (804-827-5276)

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Fill out the online form – click here (link to form – see form text below)

Links and Resources:

Opt-Out Form (see form text below)

General Informational Flier (link to pdf of general flier)

Potential Benefits of Giving Plasma Early (link to pdf slide 19)

Potential Risks of Giving Plasma Early (link to pdf slide 20)

Exception to Informed Consent (link to pdf slides 15-18)

Study PowerPoint Presentation (link to pdf of presentation, slides 1-23)

Clinical Investigators (link to pdf page of investigators)

Link to upcoming discussion meetings

Opt out online form (REDCap form):

I choose to ***NOT*** participate in VCU's Plasma study and would like to request a bracelet to wear while the study is active. It is anticipated that the study will continue through 2015.

Name:

Address:

City:

State:

Zip Code:

Phone Number (with area code):

Email:

Number of bracelets requested:

After hitting submit button, following text will appear:

Thank you for filling out the opt-out form for VCU's Plasma study. Someone from VCU will contact you to confirm your address prior to sending the bracelet to you. If you should have any questions, please call 804-82-PLASMA (804-827-5276) or email plasmastudy@vcu.edu

Thank you.

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APPENDIX 3

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
1401 Rockville Pike
Rockville, MD 20852-1448

Meeting Response Memorandum

Our Reference: CRMTS #8642
Ref. # PS001773

Division of Blood Applications

TODAY'S DATE: October 5, 2012 **PAGES:** 4

TO: Susan D. Roseff, M.D.
Virginia Commonwealth University
Fax number: (804) 828-2869
Email address: sroseff@mcvh-vcu.edu

FROM: Sonday L. Kelly, M.S.
Regulatory Project Manager
Division of Blood Applications
OBRR
Phone number: (240) 507-8446
Fax number: (301) 827-2857

SUBJECT: Summary of FDA Internal Meeting

PRODUCT: Thawed Plasma (TP)

We completed our review of your information package for Thawed Plasma (TP) and are providing the following responses to the questions you posed in the package. Although we continue to reserve Thursday, October 11, 2012, 4:30 p.m. – 5:30 p.m. for a teleconference with you regarding this product, if you find that our attached responses and advice are sufficiently clear and complete to obviate the need for further discussion, please inform us as soon as possible so that we may clear the meeting time. Alternatively, if you have questions regarding specific responses or advice, please inform us so that the appropriate members of the review team can provide clarification during the reserved meeting time.

THANK YOU

Questions from the Sponsor:

Sponsor Question 1:
Is IND necessary in this case? The same patients would be receiving TP upon arrival in the emergency department for the same indication; however, *the setting and personnel administering the plasma are different. In addition, the TP will be transported in emergency vehicles (under authority of different ambulance authorities, though the medical directors are also employees of our institution) within a locked refrigerator (electronic code required for opening) which will maintain the plasma at the appropriate/required temperature (1-6 °C). In exploratory questions with the Clinical Review Branch in the Office of Hematology, prior to submission of the research protocol, they brought up the possibility that TP used in this manner might be considered a "novel application," requiring IND.*

FDA Response to Question 1:
Yes. An IND is necessary in any clinical investigation to be conducted under Exception from Informed Consent (21CFR50.24) in which allocation to treatment (randomization in this IND) differs from standard medical practice, i.e., prehospital fluid resuscitation limited to intravenous crystalloid solution.

Sponsor Question 2:
Form 1571, box 12, item 7 (chemistry, manufacturing and control data): Our institution obtains blood products (including TP) from the local blood supplier, which is FDA licensed to manufacture plasma.

What information should we supply here?

FDA Response to Question 2:
You may provide the name and location of the local blood supplier.

Please note, as of October, 2012, FDA has issued a new Form FDA 1571 which can be accessed here: http://www.fda.gov/AboutFDA/ReportsManualsForms/Forms/default.htm

Sponsor Question 3:
Form 1571, box 12, item 8 (pharmacology and toxicology data): This data doesn't exist, to our knowledge, for TP.

FDA Response to Question 3:
For all items that do not apply to your IND, you may say "not applicable".

Sponsor Question 4:
Form 1571, box 12, item 9 (previous human experience): TP is widely used in humans who have experienced polytrauma. Again, we are not sure how to answer this question in relation to an FDA-licensed blood product.

FDA Response to Question 4:

Please see FDA Response to Question 3.

Sponsor Question 5:
Form 1571, box 9: Has an IND been previously submitted for thawed plasma (TP)? We are not aware of this. If so, would referring to this be helpful?

FDA Response to Question 5:
No, you need only to refer to an IND if you are using information from that IND.

Sponsor Question 6:
Form 1571, box 12, item 5 (investigator's brochure): What is the investigator's brochure? What elements are required?

FDA Response to Question 6:
Please see 21 CFR 312.55 *Informing investigators* and 21 CFR 312.23 *IND content and format* to determine if this is required for your IND.

Sponsor Question 7:
Form 1571, box 12, item 10: What other additional information would you suggest us supplying for this IND?

FDA Response to Question 7:

Please find below a synopsis of the additional information that must be included in the IND:

1. This trial will be conducted under Exception from Informed Consent and needs to be in compliance with 21 CFR 50.24. Please refer to FDA's Guidance for Institutional Review Boards, Clinical Investigators, and Sponsors: Exception from Informed Consent Requirements for Emergency Research, which can be found at: www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM249673.pdf

2. Please provide an outline of the overall clinical development plan.

3. Please include the following items in your protocol:
    a. A description of how this trial meets the requirements of 21CFR50.24, including prospect of direct benefit for enrolled subjects as a result of prehospital administration of 2 units Type A thawed plasma
    b. A description of the objectives and hypotheses of your study and how the study is designed to address these issues
    c. A description of the target population (enrollment criteria), including a discussion of how you will avoid enrolling patients with unsalvageable injuries
    d. A description of Stage 2 and how results from Stage 1 will be used to assess feasibility and trial design of Stage 2
    e. A description of the primary (or co-primary) and secondary endpoints
    f. Justification of the randomization method and schedule

g. A statistical analysis plan
h. Guidelines for inhospital medical management, including transfusion triggers
i. Explicit definitions of expected serious adverse reactions and a detailed safety monitoring schedule
j. Please indicate whether packed cells will be available to be administered in the ambulance
k. Please include field-to-ED transit times (mean ±SD, range) and average volume of intravenous fluids administered (mean ±SD, range) in the prehospital setting.

Sponsor Question 8:
Form 3674: Is this for required?
Certification statement. Do we check box A if we don't refer to any clinical trials in our application?

FDA Response to Question 8:
Yes, this form is required. Yes, you may check box A if you do not reference a clinical trial in your application.

END

Radio ad/psa
30-second
Community Consultation

General announcement

What **YOU** should know about participating in clinical research without **YOUR** consent: If you have been hurt and are bleeding, you may get plasma in the ambulance.

Virginia Commonwealth University is proposing a study to see if survival improves for patients who get thawed plasma by ambulance personnel before reaching the hospital. Plasma is administered routinely in hospital for those who have lost a lot of blood but is not carried by EMS.

Due to the severity of injuries, **patients may not be able to provide consent**. If you do not wish to participate you may request an opt-out bracelet.

We encourage you to learn more by visiting **go.vcu.edu/plasma** or calling **804-xxx-xxxx**.